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Fibroblast growth factor receptor (FGFR) inhibitor rogaratinib in patients with advanced pretreated squamous-cell non-small cell lung cancer over-expressing FGFR mRNA: The SAKK 19/18 phase II study

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ABSTRACT

Background: Patients with advanced squamous-cell lung cancer (SQCLC) frequently (46%) exhibit tumor over-expression of fibroblast growth factor receptor (FGFR) messenger ribonucleic acid (mRNA). Rogaratinib is a novel oral pan-FGFR inhibitor with a good safety profile and anti-tumor activity in early clinical trials as a single agent in FGFR pathway-addicted tumors. SAKK 19/18 determined clinical activity of rogaratinib in patients with advanced SQCLC overexpressing FGFR1-3 mRNA.

Methods: Patients with advanced SQCLC failing standard systemic treatment and with FGFR1-3 mRNA tumor overexpression as defined in the protocol received rogaratinib 600 mg BID until disease progression or intolerable toxicity. A 6-months progression-free survival rate (6mPFS) ≤15 % was considered uninteresting (H0), whereas a 6mPFS ≥38 % was considered promising (H1). According to a Simon 2-stage design, 2 out of 10 patients of the first stage were required to be progression-free at 6 months. Comprehensive Genomic Profiling was performedusing the Oncomine Comprehensive Assay Plus (Thermo Fisher Scientific).

Results: Between July 2019 and November 2020, 49 patients were screened and 20 were classified FGFR-positive. Among a total of 15 patients, 6mPFS was reached in 1 patient (6.7 %), resulting in trial closure for futility after the first stage. There were 7 (46.7 %) patients with stable disease and 5 (33.3 %) patients with progressive disease. Median PFS was 1.6 (95 % CI 0.9–3.5) months and median overall survival (OS) 3.5 (95 % CI 1.0–5.9) months. Most frequent treatment-related adverse events (TRAEs) included hyperphosphatemia in 8 (53 %), diarrhea in 5 (33 %), stomatitis in 3 (20 %) and nail changes in 3 (20 %) patients. Grade ≥3 TRAEs occurred in 6 (40 %) patients. No associations between mutational profile and treatment outcome were observed.

Conclusion: Despite preliminary signals of activity, rogaratinib failed to improve PFS in patients with advanced SQCLC overexpressing FGFR mRNA. FGFR inhibitors in SQCLC remain a challenging field, and more in-depth understanding of pathway crosstalks may lead to the development of drug combinations with FGFR inhibitors resulting in improved outcomes.

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1. Introduction

The fibroblast growth factor receptor (FGFR) pathway plays an important role in tumour pathophysiology by regulating cell proliferation and survival, metastatic spread and angiogenesis [1]. The role of the FGFR tyrosine kinase family as oncogenic drivers is more complex and heterogeneous compared to EGFR, BRAF, ALK, ROS1, NTRK and the likes. FGFR genetic alterations include the most common FGFR3 R248C/S249C point mutation occurring in 20 % of advanced bladder carcinomas [2] as well as less frequent FGFR3 fusions [3] and FGFR2/3 rearrangements occurring in 14 % of intrahepatic cholangiocarcinomas [4]. Beyond FGFR2 gene fusions in intrahepatic cholangiocarcinoma, the prevalence of FGFR gene fusions is exceedingly low in solid malignancies [5]. In human squamous lung cancer (SQCLC) models, amplification of FGFR1 has been demonstrated in up to 21 % of cases [6–8]. Accordingly, tumor FGFR mRNA expression has been suggested to be a superior biomarker for FGFR tyrosine kinase inhibitors to select for FGFR-dependent tumors at a time when FGFR3 mutations and FGFR2 fusions were just being identified as strong predictive factors for this class of drugs [9]. Various FGFR inhibitors including AZD4547, infigratinib or BGJ398 had limited activity with average response rates below 10 % in FGFR1 amplified SQCLC and solid tumor patients [10,11]. Rogaratinib is a novel, highly specific, and potent orally available small-molecule inhibitor of the kinase activity of FGFR1–4 [5,12,13]. High tumour *FGFR* mRNA expression levels were explored as an alternative biomarker selection strategy in preclinical models. They showed strong correlation with response to rogaratinib, independently of tumor type and *FGFR* subtype overexpression. In a first-in-man trial, objective responses to rogaratinib were observed in 10/15 (66.7 %) FGFR mRNA-positive patients without apparent FGFR genetic alteration, including one patient with SQCLC [9]. The prevalence of FGFR1–3 mRNA-positive tumors ranges from 2 % in colorectal carcinoma to 57 % in head-and-neck squamous-cell cancer, and has shown to be 47 % for SQCLC [9]. We examined early clinical activity of the oral FGFR tyrosine kinase inhibitor rogaratinib in patients with advanced SQCLC failing standard systemic treatment and being selected for tumor FGFR1-3 mRNA overexpression.

2. Methods

2.1. Study design and participants

This open-label, multi-centre, non-randomised phase 2 trial explored preliminary clinical activity of rogaratinib in a preselected patient group with the following characteristics: Patients were aged ≥18 years with radiologically measurable or clinically evaluable, locally advanced or metastatic NSCLC with squamous-cell or predominantly squamous-cell histology. All patients had to have high FGFR1-3 mRNA expression levels based on central analysis of archival (<6 months old) or fresh tumor biopsy specimens, with high expression defined as ≥1 FGFR isoform with RNA-scope scores of 3 or 4. Patients had an Eastern Cooperative Oncology Group performance status of ≤2, and they have failed standard systemic therapy for locally advanced or metastatic disease. Detailed eligibility criteria can be found in the supplemental material.

2.2. Study treatment and procedures

Rogaratinib was administered orally at a dose of 600 mg twice daily (BID) in continuous 4-weekly treatment cycles. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or study withdrawal at the investigator's discretion. Local investigator assessment of tumour response was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 after every 8 weeks. Detailed procedures including description of translational analyses can be found in the supplemental material. All protocol amendments were approved by the respective competent authorities and local review boards (Fig. 1).

2.3. Objectives and statistical analysis

The primary objective of the trial was to determine the clinical activity of rogaratinib in patients with advanced SQCLC overexpressing FGFR1-3 mRNA with the primary endpoint being progression-free survival at 6 months (6mPFS) after registration. Secondary endpoints Included objective response (OR) according to RECIST v1.1, progression-free survival (PFS), overall survival (OS), AEs according to CTCAE v5.0 and translational aspects in consenting patients. A Simon two-stage minimax design was used along with Herndon's approach to pursue patient accrual while analysing the first stage at the same time. For the primary endpoint of 6mPFS, a rate of ≤15 % was considered uninteresting while a 6mPFS rate of ≥38 % was considered promising. With a significance level of 5 % and power of 80 %, a total of 23 patients were required for the full Simon 2-stage design, Including 10 patients for the first stage and at least 13 for the second stage. The critical value for the first stage was one patient to be progression-free at 6 months. SAS 9.4 (SAS Institute Inc) and R v4.0 were used for analyses (Fig. 2).

3. Results

Between June 2019 and November 2020, 49 patients were screened for tumor FGFR status, from which 20 patients (40.8 %) were classified FGFR-positive and 15 patients were registered for the trial. High mRNA expression was found for FGFR1 in 1 patient, FGFR2 in 6 patients and

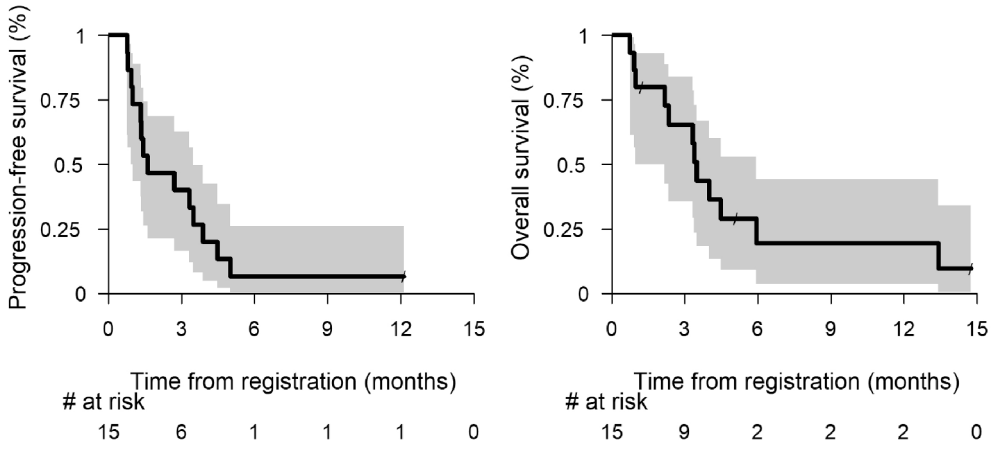

Fig. 1. Kaplan-Meier plots for PFS and OS.

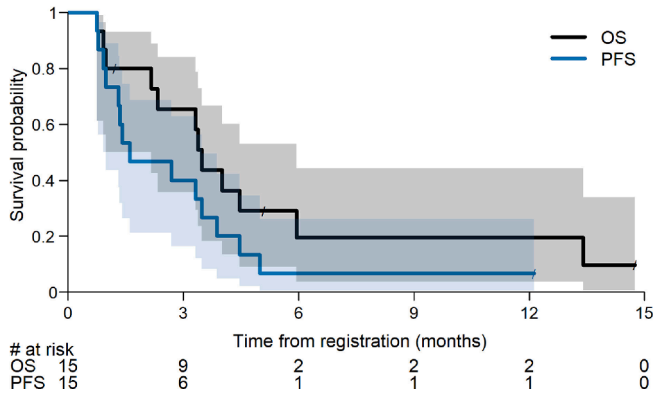

Fig. 2. Kaplan-Meier plot for PFS and OS (version 2: one plot -colored).

Table 1
Patient Demographics and Clincal Characteristics.

Patient characteristics		N	%
Gender			
male		13	86.7
female		2	13.3
Median age (years) (min, max)	66 (32, 77)		
WHO performance status			
0		4	26.7
1		8	53.3
2		3	20.0
Smoking status			
current smoker		2	13.3
former smoker		12	80
non-smoker		1	6.7
Gilberts disease			
no		15	100.0
yes		0	0.0
Hepatic metastases			
no		8	53.5
yes		7	46.7
TNM stage at registration			
IIIB		2	13.3
IVA		1	6.7
IVB/C		12	80.0
mRNA expression			
high FGFR 1 + 3		1	6.7
high FGFR2		3	20.0
high FGFR 2 + 3		3	20.0
high FGFR 3		8	53.3

FGFR3 in 12 patients. Patient and tumour characteristics are summarised in Table 1. An interim efficacy analysis was performed in the first 10 patients. Since only one patient achieved 6mPFS, the trial was closed prematurely due to futility. Among all 15 patients of the FAS, 6mPFS was reached in 1 (6.7 %) patient (90 % CI 0.3–27.9 %). There were 7 (46.7 %) patients with sable disease, 5 (33 %) with progressive disease and 3 (20 %) patients unevaluable for response. Median PFS was 1.6 (95 % CI 0.9–3.5) months, median OS was 3.5 (95 % CI 1.0–5.9) months. Median duration of study treatment was 1.4 (range 0.4–6.6) months, treatment compliance was 97.7 % (range 71.7–100 %). Main reasons for treatment discontinuation included disease progression in 9 (60 %) patients, death in 2 (13.3 %) patients and patient's decision, physician's decision and treatment delay for > 28 days in one patient each. Both deaths during trial treatment were unrelated to rogaratinib (Fig. 3 and Fig. 4).

Most frequent TRAEs included hyperphosphatemia in 8 (53 %), diarrhea in 5 (33 %), stomatitis in 3 (20 %), nail changes in 2 (13.3 %) patients (Table 2). In short, if the product of serum calcium and serum phosphate ($Ca \times PO_4$) exceeded 70 mg^2/dl^2, rogaratinib was paused and standard phosphate chelators were given at the investigator's discretion. This resulted in reversal of hyperphosphatemia within 1 week in all patients. Grade ≥3 TRAEs occurred in 5 (33.3 %) patients, including grade 3 anemia, diarrhea, nail infection, anorexia and hypercalcemia in a single (6.7 %) patient each. There were no treatment-related deaths. One patient discontinued study therapy for a TRAE. Nine (60 %) patients experienced a dose reduction of rogaratinib. Rogaratinib relative dose adherence was 97.7 %. SAEs were reported in 16 cases and 9 patients (60 %). SAE's included infections in 4 cases, respiratory disorders in 3 cases, vascular disorders in 2 cases, tumor pain and spinal fracture in a single case each. None of the SAE's were related to rogaratinib (Fig. 5). Mean TMB across all samples was 8.7 mutations per megabase (Mb), ranging from 0.95 to 17.9 mutations per Mb. No correlation between TMB and clinical outcome was found, including the only patient with a PFS of >12 months (supplementary Fig. 1). The most frequently altered gene was TP53 with a total of 17 pathogenic SNVs, insertions, and deletions detected across 14 samples. Other SNVs and Indels in genes associated with SQCLC were observed in such as NFE2L2, FBXW7, PIK3CA, ARID1A, KEAP1, and PTEN. One patient (UPN05) showed a KRAS p.G12D hotspot mutation, indicating co-occurrence of additional driver mutations in this cohort of FGFR-driven SQCLCs. Overall, we observed several molecularly distinct groups within this cohort. The first 6 cases (40 %) were characterised by the presence of co-occurring deletions of CDKN2A, CDKN2B, and MTAP on chromosome 9p. In four of these cases (67 %), additional co-occurring amplifications of PIK3CA were observed (Supplementary Fig. 2), including one patient with BRAF:

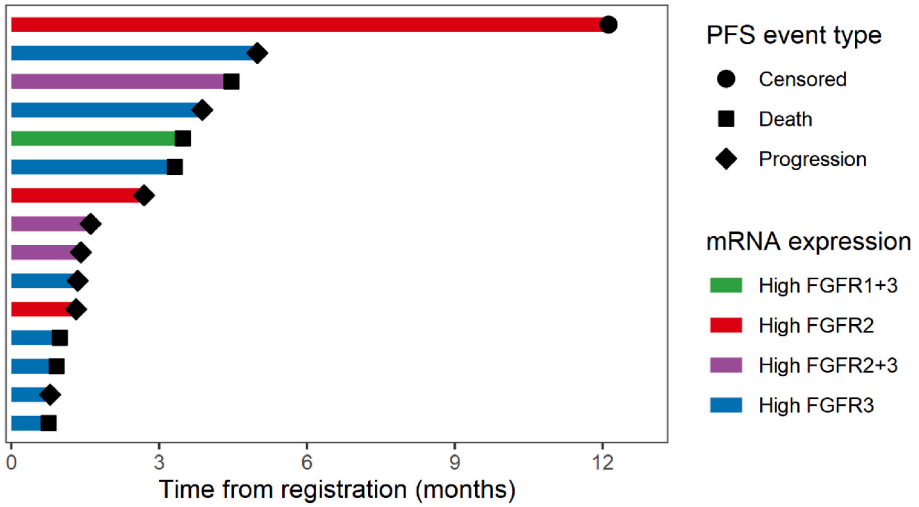

Fig. 3. Swimmer plot for PFS (version 1: colored).

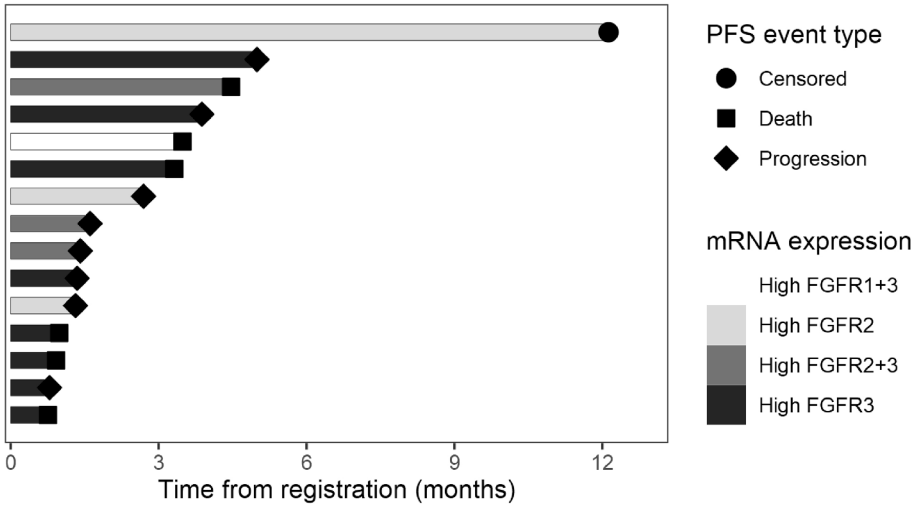

Fig. 4. Swimmer plot for PFS (version 2: black-white).

Table 2
Safety and tolerability of rogaratinib: treatment-emergent adverse events by CTCAE v.5.0 as observed in > 10 % of all patients.

Term	Grade 1		Grade 2		Grade 3		Total (N = 15)	
	N	%	N	%	N	%	N	%
Hyperphosphatemia	2	13.3	6	40.0			8	53.3
Diarrhea	3	20.0	1	6.7	1	6.7	5	33.3
Dysgeusia	2	13.3	1	6.7			3	20.0
Stomatitis			3	20.0			3	20.0
Anemia			1	6.7	1	6.7	2	13.3
Anorexia	1	1.6			1	6.7	2	13.3
Dry moth	2	13.3					2	13.3
Dry skin	2	13.3					2	13.3
Fatigue			2	13.3			2	13.3
Hypercalcemia					2	13.3	2	13.3
Nail changes	2	13.3					2	13.3

p.G469A mutation and FGFR1 amplification. The other two cases (27 %) harbouring chromosome 9p losses displayed co-occurring amplifications of CCND1, FGF3, FGF4, and FGF19, respectively. No clear associations between mutational profile and treatment outcome were observed (Supplementary Fig. 1). Notably, we observed a weak correlation between PD-L1 and cMYC (Supplementary Fig. 3). No correlation was observed between PFS and either of the immunohistochemistry markers and between TMB and PD-L1 (Supplementary Fig. 2).

4. Discussion

SAKK 19/18 studied the efficacy of the selective pan-FGFR inhibitor rogaratinib in patients with SCQLC selected for mRNA overexpression. Preclinical studies identified tumour FGFR1–3 mRNA expression as a robust predictor of rogaratinib response, including in models devoid of FGFR genetic aberrations [13]. No objective responses were documented in our study, with 7 patients (46.7 %) experiencing disease stabilization as best response. One out of 15 patients reached the primary study endpoint of 6mPFS, leading to premature closure of the study for futility. A potential reason for the limited activity may have been that the study allowed the use of archival tumor tissue not older than 6 months for the assessment of the FGFR1-3 mRNA status. This could have allowed the inclusion of patients with tumors that had lost their FGFR-dependency over the course of treatment prior to study registration. In addition, genetic co-alterations could have negatively impacted treatment activity. However, in our in-depth molecular analysis, the observed patterns and frequency of genomic alterations were in line with previous findings in SQCLC [14]. No clear associations between mutational profile and treatment outcome were observed. Potential mechanisms of resistance to FGFR-directed anticancer drug treatment are currently been looked at, including alterations in PIK3CA, RAS, cMET by high-throughput mRNA sequencing, MYC pathway activation by mRNA expression (RNAscope) and the immune microenvironment. FGFR inhibitors in squamous-cell carcinomas therefore remain a challenging field and there has not been enough evidence so far to claim that genetic alterations in FGFR are druggable drivers in SQCLC, unlike specific FGFR genetic alterations in bladder cancer and cholangiocarcinoma.

A first prospective study in SQCLC exploring the efficacy of an anti-FGFR was the S1400D, a biomarker-driven therapeutic substudy of Lung-MAP. In that study the FGFR inhibitor, AZD4547, activity was assessed in patients with SQCLC harbouring FGFR1-3 alterations (amplification. mutation, fusions) [15]. Ninety-two patients were assigned to S1400D, 43 were enrolled, and 27 AZD4547-treated patients were evaluable. Despite being well tolerated, the ADZ4547 activity was rather modest with 1 patient with FGFR3 S249C and 1 patient with FGFR1 amplification who had a partial response (7.4 %). Median PFS and OS for the AZD4547-treated cohort were 2.7 months (95 % CI: 1.4–4.5 months) and 7.5 months (95 % CI: 3.7–9.3 months), respectively. The negative results were partially explained by the biological complexity of SQCLC and by the fact that FGFR amplifications are biologically different from FGFR fusions or mutations in that they represent a potentially heterogeneous aberration. Given their results and our trial, more in-depth understanding of pathway crosstalks and subsequent molecular sub-categorization of SQCLC are needed may allow to explore drug combinations with FGFR inhibitors in the future.

The higher proportion (40.8 %) of tumor FGFR mRNA-positivity observed in our trial compared to genetic alterations of the FGFR pathway can be explained by the overexpression of FGFRs in the absence of genetic alterations, epigenetic dysregulation and/or transcriptional dysregulation or non-coding alterations [16,17]. The importance of these non-genetic mechanisms was corroborated by preclinical data showing that nearly half of the tested infigratinib-sensitive cell lines have no apparent FGFR genetic alterations [18]. In a previous rogaratinib phase 1 clinical study, no DLTs were observed up to a dose of 800 mg BID given continuously [10]. Rogaratinib-induced, dose-dependent hyperphosphatemia occurred in patients treated above 400 mg BID due to on-target inhibition of the FGF23-FGFR1-Klotho system involved in renal phosphate homeostasis [19]. This most frequent TRAE is a class-effect of FGFR1-targeting drugs and well manageable with rogaratinib dose reductions and standard phosphate chelators. Limitations of this study include the limited sample size, the unvalidated cut-off values for

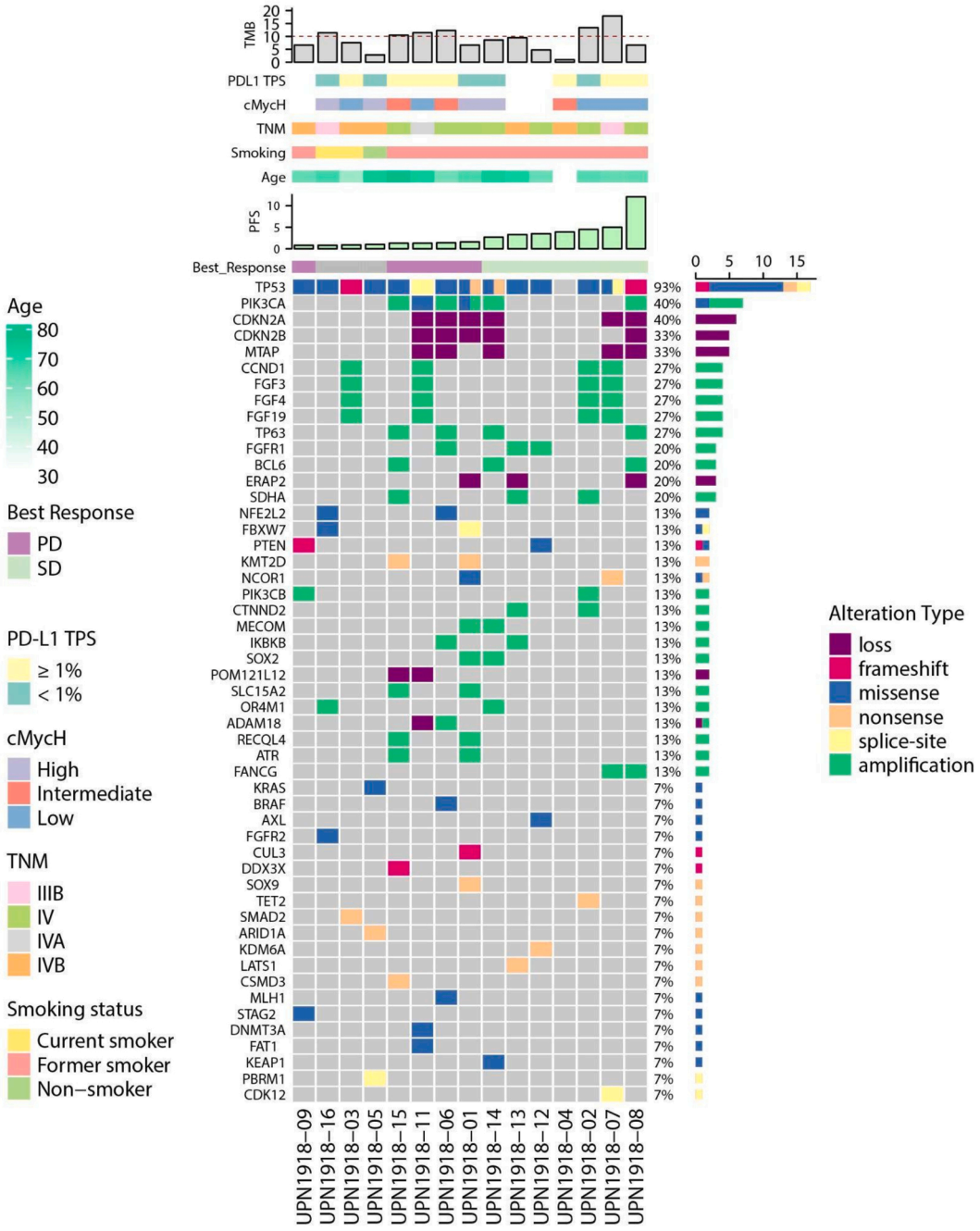

Fig. 5. Analysis for genomic alterations across the 15 patients.

the determination of FGFR mRNA overexpression, the heterogeneity regarding prior systemic anticancer treatment in study patients, and the potential bias from biomarker selection in archival tumor tissue.

5. Conclusions

Rogaratinib monotherapy had limited activity in patients with heavily pretreated, advanced SQCLC overexpressing tumor FGFR1-3 mRNA. FGFR inhibitors in squamous-cell carcinomas remain a challenging field. More in-depth understanding of pathway crosstalks are warranted and may allow future drug combinations with FGFR inhibitors or even deeper selection of SQCLC.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **AA:** Advisory board: MSD Oncology, Roche, Takeada, Pfizer, Bristol-Myers Squibb, AstraZeneca, Eli-Lilly, Roche. Speaker Bureau: Eli-Lilly, AstraZeneca, Amgen. **SA** Consulting or Advisory Role**:** Bristol Myers Squibb, AstraZeneca, Boehringer Ingelheim, Eisai, Roche, Novartis, Merck Serono, MSD Oncology, Pfizer, Takeda, AbbVie, Research Funding**:** Boehringer Ingelheim, AstraZeneca, Bristol Myers Squibb, Eisai, Merck Serono, AbbVie.Expert Testimony: Roche, AstraZeneca, Bristol Myers Squibb. Travel, Accommodations, Expenses**:** Roche Pharma AG, Lilly, Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Amgen **LH**: no conflict of interests, MS: no conflict of interests **CW**: no conflict of interests. **SH**: no conflict of interests. **MK**: Consulting or Advisory role:

Roche, AstraZeneca, Takeda, BMS, MSD Oncology. Travel, Accommodations, Expenses: Pfizer, Roche, Takeda **EF**: no conflict of interests. **NM**: Stock and Other Ownership interests: MaxVAX SA Research Funding: MaxiVax Patents, Royalties, Other Intellectual Property: I am an inventor on patent owned by MaxiVAX SA and on patent co-owned by Geneva University Hospital and MaxiVAX SA Uncompensated Relationships: MaxiVax. **LM**: Consulting or Advisory Role: Takeda, Roche, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer Travel, Accommodations, Expenses: Takeda, Bristol Myers Squibb, Merck, Roche, AstraZeneca **PJ**: no conflict of interests. **IA**: no conflict of interests. **BC**: no conflict of interests. **SSP**: Honoraria: Novartis Consulting or Advisory Role: Diaceutics Ireland Limited, Merck (Schweiz) AG, AstraZeneca AG **MJ**: Consulting or Advisory Role: Novartis, AstraZeneca, Basilea Pharmaceutical, Bayer, Bristol Myers Squibb, Debiopharm Group, Merck, Roche, Sanofi. Research Funding: AstraZeneca, Basilea Pharmaceutical, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Immunophotonics, InnoMedica, Janssen Oncology, Lilly, Merck, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Takeda. **MF** Consulting or Advisory Role: BMS, AstraZeneca, MSD, Takeda, Roche, Lilly Speakers' Bureau: Pfizer Research Funding: BMS, AstraZeneca.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.08.016.

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